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EVALUATION OF THE ANTIBACTERIAL ACTIVITY OF CYNARA SCOLYMUS EXTRACT AND ITS WOUND HEALING POTENCY AGAINST MULTIDRUG-RESISTANT *ACINETOBACTER BAUMANNII*, *IN VITRO* AND *IN VIVO* STUDY

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ABSTRACT

Objectives: Plants extracts known as phytomedicine have immense potential for the management and treatment of wounds. Aim of this study was evaluate the antimicrobial effect and wound healing potency of *Cynara scolymus* against multidrug-resistant *A. Baumannii* infection.

Materials and Methods: *Cynara scolymus* hydroalcoholic extract in comparison with gentamicin antibiotics on clinical strains as well as pathogenic bacteria such as Multidrug-Resistant *Acinetobacter Baumannii*, under *in vitro* conditions using micro broth dilution and disc diffusion methods. Moreover, minimum inhibitory concentration and Minimum bactericidal concentration of its hydroalcoholic extract was also evaluated.

Results: The results showed that although *Cynara scolymus* extract was effective on Multidrug-Resistant *Acinetobacter Baumannii*. The extract was also tested in the form of topical administration on excision wound model in rats. In the extract-treated wounds, the wound healing percent was significantly increased in comparison with controls.

Conclusions: Based on this research, herbal extract of *Cynara scolymus* can be a great candidate for the treatment of Multidrug-Resistant *Acinetobacter Baumannii* infections and merits further studies.

KEYWORDS: : multidrug-resistant, *acinetobacter baumannii*, wound healing, *cynara scolymus*, animal study

INTRODUCTION

Skin refers to the soft tissues on the surface of the body, and its weight accounts for about 15% of total body weight. It can therefore be said that skin

is the largest organ of the human body. In daily life, skin mainly isolates the internal and external environments of the human body to avoid physi-

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cal, chemical, and microbial invasions, thereby protecting the body. In addition, skin also has functions such as regulating the body temperature and metabolism. However, it will become susceptible to a variety of external factors, such as mechanics, heat and chemical reagents, that may cause wounds of different types. If deep wounds or burns are encountered, the ability of skin to heal itself is far from sufficient, and these hard-to-heal wounds may ultimately result to severe risks such as amputation or death. Traditional wound management is limited by what is immediately at hand or can be acquired locally, such as water, soil, and plant and animal products, and is frequently complemented with ceremony and ritual as an added measure. For millions of people across Asia, Africa, the Middle East, and Latin America, traditional medicines derived from local plants, animals, and natural products are the mainstay of wound care; for some, it is the only source of wound care [Thakur R et al., 2011; Murphy P, Evans G 2012]. Plants have the immense potential for the management and treatment of wounds. A large number of plants are used by tribal and folklore in many countries for the treatment of wounds and burns. These natural agents induce healing and regeneration of the lost tissue by multiple mechanisms. These phytomedicine are not only cheap and affordable but are also safe [Trop M et al., 2006].

Cynara scolymus L or artichokes is a perennial plant native to the Mediterranean region a variety of a species of thistle cultivated as a food. Both wild forms and cultivated varieties (cultivars) exist. This vegetable grows to 1.4–2 m tall, with arching, deeply lobed, silvery, glaucous-green leaves 50–82 cm long. This plant was traditionally used as a food among the ancient Greeks and Romans [Kader M et al., 2014; Salekzamani S et al., 2019]. In North Africa, where it is still found in the wild state, the seeds of artichokes, probably cultivated, were found during the excavation of Roman-period Mons Claudianus in Egypt [Vamanu E et al., 2011; Oliveira G et al., 2014]. *Cynara scolymus* is a pharmacologically important medicinal plant containing phenolic acids and flavonoids. Experimental studies indicate antioxidant and hepatoprotective effects of *C. scolymus* but there have been no studies about therapeutic effects of liver diseases. *Cynara scolymus* L. (Asteraceae) (artichoke) is commonly eaten

as a vegetable; its leaves are frequently used in folk medicine in the treatment of hepatitis, hyperlipidemia, obesity and dyspeptic disorders [Oliveira G et al., 2014; Miraj S, Kiani S., 2016].

Wound healing entails a multi-step process involving inflammation, proliferation, and remodeling. During the complex healing process, the most critical concern in skin wound is bacterial infections, which can be triggered by the accumulation and growth of bacterial cells at wound sites. The common causative bacteria associated with wound infections include *Staphylococcus aureus* (*S. aureus*), methicillin-resistant *S. aureus* (MRSA), *Acinetobacter baumannii* (*A. baumannii*), *Pseudomonas aeruginosa* (*P. aeruginosa*), etc. Bacterial infections at wound sites are known to cause delayed wound healing and, in some cases, may result in serious detrimental effects that can endanger life [Badie O et al., 2022].

Acinetobacter baumannii, which belongs to the most serious multidrug-resistant (MDR) ESKAPE pathogens, including *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter spp.*, has globally acquired the attention of the medical field as a public health threat. This attention is due to its ability to cause nosocomial infection, especially in intensive care units (ICU), and to develop multiple resistance mechanisms [Mihu M, Martinez L, 2011]. It is involved in a number of hospital-acquired infections including pneumonia, bacteremia, urinary tract infections, meningitis and wound infections. Unfortunately, multidrug-resistant *A. baumannii* is usually related to prolonged hospital accommodation, a high possibility of ICU admission and high morbidity and mortality rates [Turner P et al., 2003]. Widespread multidrug-resistant *A. baumannii* has been observed along with the availability of many classes of antibiotics to which *A. baumannii* has shown resistance. This case prompted the World Health Organization (WHO) to include *A. baumannii* in the list of the antibiotic-resistant priority pathogens, categorizing it according to the urgency of the need for new antibiotics as “critical”. In addition, the Centers for Disease Control and Prevention (CDC) has supported focusing on drug discovery for infections of the highest need for those caused by *A. baumannii*, considering it

as an “urgent threat” [Badie O et al., 2022]. The emerging multi-drug resistance and the deficiency of suitable antibiotics have demanded a search for novel antibacterial agents.

The presence of various life-sustaining constituents in plants has urged scientist to examine these plants with a view to determine potential wound healing properties. So, in this study, we evaluated the antimicrobial effect and wound healing potency of *Cynara scolymus* against multidrug-resistant *A. Baumannii* infection in an animal model.

MATERIALS AND METHODS

Clinical strains and Minimum inhibitory concentration: Nine clinical strains of *A. baumannii* were collected from Amir-al-Momenin (A.S) hospital, Arak. Iran. MDRAB (drug-resistant *A. baumannii*) strains were defined. *Escherichia coli* (ATCC 25922) used as control negative.

Antibiotic susceptibility testing: All clinical isolates of *A. baumannii* were screened for antimicrobial activity by the disc diffusion method on Muller-Hinton agar plates with Penicillin, Amoxicillin, Gentamicin, Tetracycline, Ciprofloxacin, Amikacin, Cefixime, Ceftazidime [Mahboob N. et al., 2020; Elzuhria A et al. 2023]. After 24 hours incubation at 37 °C, the diameters of the zones of complete inhibition were measured from the back of plates with ruler and the results of the antibiotics were compared with Clinical Laboratory Standards Institute 2022(CLSI).

Minimum inhibitory concentration (MIC)

All the isolates were subjected to Minimum inhibitory concentration testing for various drugs using the CLSI 2023 (Clinical and Laboratory Standards Institute) guidelines [CLSI M100 (2023)]. Minimum inhibitory concentration test was performed in sterile 96-well plates by micro broth dilution method [Kader M et al., 2014]. Briefly, 100 µl of culture medium of Mueller-Hinton broth (Merck, Germany) were poured into 96-well micro plates and serial dilutions were made. In another row, in accordance with the tested bacteria sensitivity, 80 µl of ciprofloxacin, gentamicin, and penicillin antibiotics were added. In the final step of the procedure, addition of 100 µl diluted microbial suspension equivalent to a 0.5 McFarland standard was performed to all the wells. After 24 hours of incubation at 37 °C temperature, the turbidity as

the evidence for the bacteria growth was recorded. According to the definition of the concentration of the last (diluted) well with no turbidity, Minimum inhibitory concentration equivalent was used and extract control section, cultivation medium, and microbes were considered separately.

Minimum bactericidal concentration (MBC): For determining Minimum bactericidal concentration, 10 µl of the three sections before Minimum inhibitory concentration was separately cultivated on Mueller-Hinton agar medium. After 24 hours, the lowest concentration of the extract in which the bacteria did not grow (99% no growth) was reported as Minimum bactericidal concentration [Kader M et al., 2014].

Plant authentication and collection: The experimental plant was verified by Plant Taxonomist, at the herbarium of the Science Faculty, Science and Research Branch, Islamic Azad University, Arak, Iran. (712-IMPH)

Preparation of *Cynara scolymus* extract: To evaluate the antimicrobial potential of *Cynara scolymus* against multidrug-resistant *A. Baumannii*, its extract was prepared using Soxhlet method [Redfern, Kinninmonth et al., 2014]. Briefly, the leaves were dried in shade and subsequently grinded. The powder (100 gr) was poured into the thimbles and were set on Soxhlet device. Distilled water was added as a solvent to 300 ml of the ethanolic mixture. Extraction was continued for 12 hours. The extract was transferred to glass containers and then in order to evaporate the remaining solvent, they were kept without the lid in the oven for 24 hours at 50 °C. the remaining powder was kept in refrigerator for subsequent experiments.

Antibacterial testing of the extract: Antibacterial properties of the *Cynara scolymus* extract was evaluated by Disk diffusion method. In this manner, the bacteria were cultivated on Mueller-Hinton agar medium. Discs contained 20 µL of the *Cynara scolymus* extract (128 g/L) were placed on Mueller-Hinton agar inoculated with 5×10^5 cfu/mL of multidrug-resistant *A. Baumannii*. Ceftazidime disk and 10 µg ciprofloxacin, and 10 µg penicillin were used as control. The tests were repeated three times and the results were presented as average.

Minimum inhibitory concentration and Minimum bactericidal concentration on the extract: In this study, to determine the minimum inhibitory

concentration and minimum bactericidal concentration that inhibits the growth of microorganisms by the micro serial dilution method in broth from serial dilutions of 50% hydroalcoholic extract of 150 mg/ml to evaluate the antimicrobial effect of this extract on the growth of the standard strain of *Escherichia coli* ATCC and 9 strains of *A. Baumannii* resistant to all drugs was used.

Fractional Inhibitory Concentration Index (FICI):

Evaluation of the fractional inhibitory concentration index of *Cynara scolymus* extracts The Muller Hinton agar dilution method was used to evaluate the Fractional Inhibitory Concentration Index [Konaté, K., et al., 2012; Apridamayanti P. et al., 2021].

Synergistic Antimicrobial Assays: Gentamicin antibiotics was used in combination with *Cynara scolymus* extract for synergistic antimicrobial assays. To determine the synergistic antimicrobial activity, the bacterial strain was spread with a turbidity of 0.5 McFarland on Mueller-Hinton agar (MHA) plates. The discs were anaerobically kept at 37 °C for 24 hours. For the assessments of the synergistic effects, selected antibiotic discs were discretely impregnated with 5 µL of different plant extracts (at the Minimum bactericidal concentration value) and employed on the inoculated agar plates. The zones of inhibition produced by the plant extract in combination with standard antibiotics after overnight incubation were estimated as described [Adwan G et al., 2010]: if zones of combination treatment > zone of plant extract + zone of the corresponding antibiotic, was interpreted as synergism; if zone of combination treatment = zone of plant extract + zone of correspondence antibiotic, was interpreted as additive; if zone of combination treatment < zone of plant extract + zone of the corresponding antibiotic, was interpreted as antagonism.

IN VIVO STUDIES

Experimental animals: In this study, Wistar male rats with the weight 150-200 g were obtained from animal house of Pasture Institute of Iran. The animals were kept in a well-controlled room in terms of temperature, light, and free access to water and food. The rats were anesthetized by ketamine (50 mg per kg body weight) and xylazine (5 mg per kg body weight).

Excision wound creation: The Wistar male

rats were anesthetized with ketamine hydrochloride solution, intraperitoneally. Hair was removed by shaving the dorsal back of the rats. Excision wounds were inflicted on the dorsal thoracic region 1–1.5 cm away from the vertebral column on either side and 5 cm away from the ear. After wound area preparation with 70% alcohol, using a sterile round seal of 2.5 cm diameter or a surgical blade or 5–8 mm biopsy punch, circular skin from the predetermined area on the depilated back of the animal was excised to its full thickness to obtain a wound area of about 280 mm² diameter and 2 mm depth. Hemostasis was achieved by blotting the wound with a cotton swab soaked in normal saline. The wound was left undressed to the open environment and no local or systemic anti-microbial agents were used. The rats were distributed in five random groups as:

- (1) Negative control group (without treatment and without multidrug-resistant *A. Baumannii* after the wound);
- (2) Positive control group (without treatment with multidrug-resistant *A. Baumannii* after the wound),
- (3) treated group with antibiotic (gentamicin - GM),
- (4) *Cynara scolymus* hydroethanolic extract-treated group (topical as in alternating days, 0.5g, based on the wound area),
- (5) Synergistic group (Herbal extract with antibiotic).

Each group included 6 rats and each rat was placed in a separate cage.

Wound healing evaluation: After surgery, the drug administration and the excision wound margins were traced at 2-day intervals. Measurements of the wounds were performed using digital imaging analysis for 21 days. Measurements were continued up to 21 days. Wound contraction was expressed as percentage of wound area that had healed. The wound surface was measured using template and caliper in alternating days to the full healing.

During measurement, each rat was imaged to measure by suitable scale and image analyzer software to control the validity of manual measurement. The wound healing percentage in various groups was measured according to the following formula:

$$WH (\%) = \frac{WL1 - WLA}{WL1} \times 100$$

where WH - Wound healing, WL1 - Wound level at the first day, WLA - Wound level on day A.

Histological evaluation: The effects of *Cynara scolymus* hydroalcoholic extract on the tissue granulation, cellular density, and extension of the fibrosis of the skin was studied by immunohistochemistry using light microscope. Histological specimens of the five groups were fixed in 10% buffered formalin, paraffin imbedded, and stained with hematoxylin and eosin (H&E) and the samples were studied pathologically.

Data analysis: Statistical analysis was performed using SPSS 16 software. All data are presented as means $\pm$ SEM. To compare multiple means in groups, one-way ANOVA followed by Tukey's post hoc comparison was used. In this article, the significance level of the range of p-values is denoted by asterisks as follows: $p > 0.05$ – n.s. (not significant), $(0.01 < p < 0.05)$ *- significant; $0.001 < p < 0.01$; ** -Highly significant; $p < 0.001$ *** - Very highly significant.

RESULTS

Results of antibiotic susceptibility tests: In the present study, initial screening was done to evaluate the antibacterial activity of selected antibiotics against multidrug-resistant *A. Baumannii*.

All of the isolates were resistant to all tested antibiotic without any zone of inhibitions.

Results of antibacterial activity of the extract: In this study, *Cynara scolymus* hydroethanolic extract have 8-11 mm zone of inhibitions on the multidrug-resistant *A. Baumannii* isolates as shown in table 1.

The results of Minimum inhibitory concentration determination showed that the extract of this plant inhibits the growth of all strains on *A. Baumannii* strains at concentrations of 150 and 75mg/ μ l (1.2 and 1.2 dilution) and the inhibitory effect was better than the extract with lower dilution in two strains no. 2 and 3, it was observed that up to a concentration of 37.5 mg/ml (1.4 dilution) controlled the growth of these two strains. Also, in the ATCC *Escherichia coli* standard strain, the concentration of growth inhibition up to 1.8 dilution and equivalent to 18.74 mg/ml of hydroalcoholic extract was obtained (Figure 1).

TABLE I.

Results of disk diffusion test of tested extract on the resistant isolates

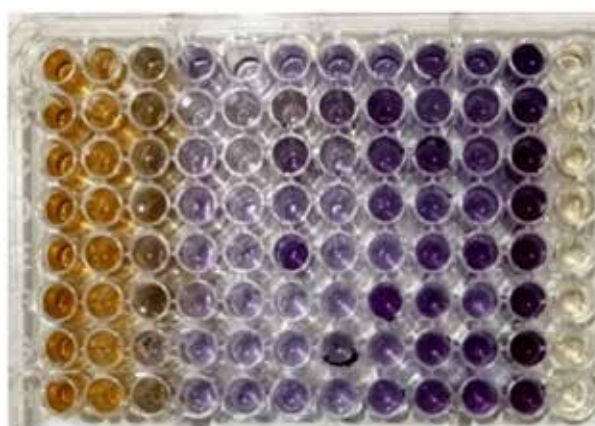
Isolate number	1	2	3	4	5	6	7	8	9
Zone of inhibitions (mm)	10	11	11	9	10	9	8	10	8

Minimum bactericidal concentration of 50% hydroalcoholic extract of artichoke plant was obtained in all strains with the same minimum inhibitory concentration inhibitory concentration and it was obtained at a concentration of 75 mg/ml for all strains of *A. Baumannii*, which was obtained in two more sensitive strains (strain 2 and 3) This concentration was obtained up to 37.5 mg/microli-ter of the extract (Figure 2).

For the standard strain of *Escherichia coli* ATCC 25922, the minimum inhibitory concentration of 18.74 mg/ml was obtained.

Synergism study of *Cynara scolymus* with Antibiotic: Results of synergism study of *Cynara scolymus* and Gentamicin showed strong synergistic activity against multidrug-resistant *A. Baumannii* (Table 2).

In investigating the interaction between sub-Mic dilutions (64 to 0.125 μ g/ml) of the antibiotic gentamicin and sub-Minimum inhibitory concentration concentrations (1 to 1.64) of 50% hydroalcoholic extract of *Cynara scolymus* against *A. Baumannii* strains resistant to all the leading drugs. Fractional Inhibitory Concentration Index was calculated and interpreted.



	1	2	3	4	5	6	7	8	9	10	11	12
A	0.447	0.378	0.352	0.864	1.864	2.014	2.404	2.663	2.078	3.265	2.395	0.059
B	0.421	0.279	1.376	1.095	1.095	2.108	2.339	2.202	2.471	2.78	3.547	0.061
C	0.524	0.554	0.70	1.324	1.324	1.962	2.035	2.277	2.584	2.476	2.933	0.06
D	0.415	0.474	0.97	1.387	1.387	2.056	2.263	2.711	2.317	2.045	2.269	0.145
E	0.526	0.238	1.095	1.682	1.682	2.171	2.131	2.297	2.179	1.938	2.988	0.054
F	0.698	0.42	1.381	2.236	2.089	2.368	2.51	2.251	2.434	2.293	3.442	0.053
G	0.385	0.514	1.292	2.711	2.563	2.66	2.623	2.666	3.286	1.884	2.804	0.42
H	0.573	0.44	1.443	1.814	1.814	2.126	2.626	2.916	2.834	3.085	2.719	0.05

FIGURE 1. Results of minimum inhibitory concentration of the extract for some of the isolates.

Based on the obtained results, the effect on the interaction between two solutions in average concentrations of 9.37 mg/ml of hydroalcoholic extract of artichoke plant and concentrations of 4, 2 and 1 µg/ml of gentamicin antibiotic can have an effect. It shows remarkable synergy to control the growth and control of these drug-resistant clinical strains.



FIGURE 2. Results of minimum bactericidal concentration of the extract for some of the isolates.

TABLE 2.

Results of synergism study of *Cynara scolymus* extract (FIC) and Gentamycin

No	SI	FIC	FICI	Mean and SD
	Antibiotics	<i>C. scolymus</i> extract		
1	E6	0.062	0.25	0.312
	F5	0.125	0.125	0.250
2	E7	0.031	0.25	0.281
	F6	0.062	0.125	0.187
3	E7	0.031	0.25	0.281
	F5	0.125	0.125	0.250
4	E5	0.125	0.25	0.375
	F4	0.25	0.125	0.375
5	E6	0.062	0.25	0.312
	F5	0.125	0.125	0.250
6	E5	0.125	0.25	0.375
	F4	0.25	0.125	0.375
7	E6	0.062	0.25	0.312
	F4	0.25	0.125	0.375
8	E5	0.125	0.25	0.375
	F4	0.25	0.125	0.375
9	E4	0.25	0.25	0.5
	F3	0.5	0.125	0.625

Notes: SI- Synergistic inhibition, FIC- Minimum inhibitory concentration, FICI - Fractional Inhibitory Concentration Index

Wound healing evaluations: The wound healing percentages in the different days of wound excision repair model in the three groups were evaluated. (Table 3a, Figure 3)

The results indicated that *Cynara scolymus* hydroethanolic extract-treated wounds epithelized faster in comparison with negative control group as measured during 21 days of treatment ($p < 0.05$). However, the differences between the *Gundelia tournefortii* L. hydroalcoholic extract- and *A. Baumannii* -treated groups were significant statistically (Table 3b). The results indicated that *Cynara scolymus* hydroethanolic extract-treated wounds epithelized faster in comparison with negative control group as measured 21 days after treatment ($p < 0.05$). However, the differences between the *Cynara scolymus* hydroalcoholic extract and *A. Baumannii* - treated groups were significant (Table 3c).

Histological results: The results showed matrix irregularity of the connective tissue and clear inflammatory reactions compared to the group receiving *Cynara scolymus* hydroalcoholic extract. negative control group had an irregular granulated tissue, more cells, and high inflammation. On 21th day of the study in *Cynara scolymus* hydroalcoholic extract-treated group, the cellular density of fibrosis tissue was low, inflammation was brief, and granulation was mature in comparison with the group which received *A. Baumannii* ointment as the scar area in *A. Baumannii* -treated group was big and irregular but epidermal progress was consistent with *Cynara scolymus* extract-treated group. We didn't observe dermal tissue re-organization differences elements in these two groups. At the end of the treatment process, the epidermis formation was intact in both groups and the scar area was smaller as well. From the pathological aspects, the tissue samples treated with *Cynara scolymus* extract had better healing quality with regular arrangement and low inflammation density and time needed for repairing. Fibroblast increased on the 14th day in the treatment group. Neutrophils increase strongly in the early stages of the wound. In the treatment group, neutrophils decreased from day 2, which was caused by the control of inflammation, which indicated the effect of the treatment (Tables 4a, 4b, 4c, Figure 4). Macrophage in the treatment group increased on days 2 and 3, which indicates the removal and control of infection on days 6 and 7 (Tables

TABLE 3A.

Mean value and standard deviation for percentage of wound healing on different days

Comparison groups	3 day	7 day	14 day	21 day
Negative control	17.8 ±0.200	52.15 ±1.15	90.00 ±1.00	98.75 ±0.25
Positive control	5.50 ±0.500	34.50 ±0.50	84.50 ±1.50	97.50 ±0.50
Antibiotic treatment	1.75 ±0.750	32.00 ±0.0	76.50 ±1.50	97.00 ±1.00
Herbal extract treatment	41.50 ±1.50	82.50 ±0.50	99.00 ±0.00	100.0 ±0.00
Extract treatment with antibiotics	34.50 ±0.50	77.50 ±1.50	98.75 ±0.25	100.0 ±0.00

TABLE 3B.

P-value (by number of stars) for percentage of wound healing on different days (within group)

Comparison groups	Days within the group			
	1 with 3	3 with 7	7 with 14	14 with 21
Negative control	0.0004***	0.0012**	0.0016**	0.0136*
Positive control	0.0082**	0.0006***	0.0010***	0.0145*
Antibiotic treatment	0.1448	0.0006***	0.0011**	0.0076**
Herbal extract treatment	0.0013**	0.0015**	0.0009***	0.3333
Extract treatment with antibiotics	0.0002***	0.0013**	0.0051**	0.0377*

TABLE 3C.

P-value (by number of stars) for the percentage of wound healing on different days (outside the group)

Comparison of groups	1 day	3 day	7 day	14 day	21 day
Negative control \ Positive control	0.0955	0.0019**	0.0050**	0.0927	0.1548
Positive control \ Antibiotic treatment	ns	ns	0.0377*	0.3333	ns
Positive control \ Herbal extract treatment	ns	0.0019**	0.0002***	0.0105*	0.0377*
Positive control \ Extract treatment with antibiotics	ns	0.0006***	0.0013**	0.0112*	0.0377*
Antibiotic treatment \ Herbal extract treatment	0.4226	0.0018**	<0.0001****	0.0044**	0.0955
Antibiotic treatment \ Extract treatment with antibiotics	0.4226	0.0008***	0.0011**	0.0046**	0.0955
herbal extract treatment \ Extract treatment with antibiotics	ns	0.0474*	0.0871	0.4226	ns

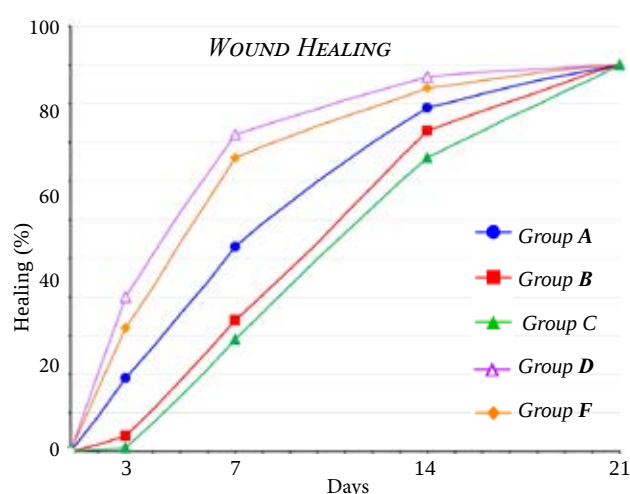


FIGURE 3. Dynamics of wound healing (in the percentage) in the studied groups (Group A – Negative control; Group B– Positive control; Group C – Antibiotic treatment; Group D – Herbal extract treatment ; Group F – Extract treatment with antibiotics) on different days.

5a, 5b, 5c, Figure 5). . Lymphocyte is for chronic infection, on the 10th day and later, by inhibiting lymphocyte production in the treatment group (Tables 6a, 6b, 6c, Figure 6), it causes the maturation of fibroblasts and the removal and control of infection (Tables 7a, 7b, 7c, Figure 7).

DISCUSSION

Wound healing is a complicated process occurring in injured tissue to restore its construction and return the damaged tissue to its normal situation as soon as possible. There are three stages for wound healing: inflammation, proliferation and remodeling of the extra cellular matrix. The proliferative phase is defined by angiogenesis, collagen deposition, epithelialization and wound contraction. The aim of the healing process is to prevent pathogens invasion, confirm the integrity of damaged tissue, and reconstruct the skin physiological function [Ezzati A et al., 2009].

INVESTIGATING NEUTROPHILS SECRETED IN WOUND TISSUE

TABLE 4A.

Mean value and standard deviation for the number of neutrophils secreted in the wound tissue on different days

Comparison groups	1 day	3 day	7 day	14 day	21 day
Negative control	195.0 ±15.00	205.0 ±20.00	110.0 ±10.00	52.50 ±4.500	17.50±2.500
Positive control	222.5 ±15.00	252.5 ±17.500	250.0 ±50.50	102.5 ±4.500	52.50±2.500
Antibiotic treatment	217.5 ±15.00	247.5 ±22.50	230.0 ±20.00	112.5 ±7.000	62.50±3.500
Herbal extract treatment	222.5 ±7.500	110.0 ±10.00	55.00 ±5.000	17.50 ±2.500	5.000±0.000
Extract treatment with antibiotics	217.5 ±12.50	97.50 ±1.500	52.50 ±2.500	11.00 ±1.000	5.000±1.000

TABLE 4 B.

P-value (by number of stars) for the number of neutrophils secreted from the wound tissue on different days (within a group)

Comparison groups	Days within the group			
	1 with 3	3 with 7	7 with 14	14 with 21
Negative control	0.2929	0.0136*	0.0307*	0.0101*
Positive control	0.0077**	0.0377*	0.0003***	0.0050**
Antibiotic treatment	0.0136*	0.0198*	0.0005***	0.0050**
Herbal extract treatment	0.0083**	0.0389*	0.0215*	0.0377*
Extract treatment with antibiotics	0.0009***	0.0061**	0.0042**	0.0267*

TABLE 4C.

P-value (by number of stars) for the number of neutrophils secreted from the wound tissue on different days (outside the group)

Comparison of groups	1 day	3 day	7 day	14 day	21 day
Negative control \ Positive control	0.0389*	0.0093**	ns	0.1056	0.0101*
Positive control \ Antibiotic treatment	0.2929	0.0513	0.0007***	0.0017**	0.1056
Positive control \ Herbal extract treatment	ns	0.0045**	0.0002***	0.0009***	0.0028**
Positive control \ Extract treatment with antibiotics	0.2929	0.0005***	0.0008***	0.0014**	0.0028**
Antibiotic treatment \ Herbal extract treatment	0.2929	0.0056**	0.0002***	0.0007***	0.0019**
Antibiotic treatment \ Extract treatment with antibiotics	ns	0.0006***	0.6985	0.1372	0.0019**
Herbal extract treatment \ Extract treatment with antibiotics	0.2929	0.3491	ns	0.1056	ns

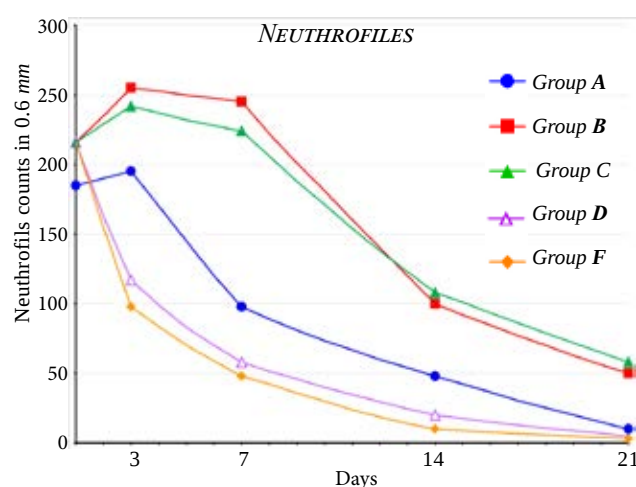


FIGURE 4. Changes in the content of neutrophils (in percent) in the studied groups (Group A – Negative control; Group B– Positive control; Group C – Antibiotic treatment; Group D – Herbal extract treatment ; Group F – Extract treatment with antibiotics) on different days.

The results of studying the inhibitory and lethal effect of *Cynara scolymus* on pathogenic strains showed that the largest diameter of the growth inhibition zone ethanolic extracts of artichoke at a concentration of 800 mg/ml belonged to multi-drug-resistant *A. Baumannii* infection.

Alcohol has a more significant ability to extract antioxidants and antibacterial, and therefore alcoholic extract is more effective than aqueous extract [Zhu X et al., 2004].

Zhu et al. evaluated the antimicrobial activity of ethanolic extract and *Cynara scolymus* ethyl acetate against 15 microorganisms, including seven species of *Bacillus subtilis*, *S. aureus*, *Agrobacterium tumefaciens*, *Micrococcus luteus*, *E coli*, *S. typhimurosa*, four species of *Polyporus albicans*, *Candida lusitaniae*, *Saccharomyces*

INVESTIGATING THE SECRETED MACROPHAGE IN THE WOUND TISSUE

TABLE 5A.

Mean value and standard deviation for the number of secreted macrophages
in the wound tissue on different days

Comparison groups	1 day	3 day	7 day	14 day	21 day
Negative control	6.000 ±1.00	7.500 ±0.500	28.50 ±1.50	56.50 ±1.50	70.00 ±1.00
Positive control	13.50 ±1.50	29.00 ±1.00	50.50 ±0.50	82.50 ±2.50	90.00 ±2.00
Antibiotic treatment	15.00 ±0.00	17.50 ±2.50	33.50 ±1.50	61.00 ±1.00	83.50±1.50
Herbal extract treatment	15.00 ±1.00	55.00 ±5.00	82.50 ±2.50	111.0 ±1.00	92.50±2.50
Extract treatment with antibiotics	14.00 ±1.00	52.50 ±2.50	71.50 ±1.50	103.0 ±3.00	89.50±0.50

TABLE 5B.

P-value (by number of stars) for the number of macrophages secreted from the wound tissue
on different days (within group)

Comparison groups	Days within the group			
	1 with 3	3 with 7	7 with 14	14 with 21
Negative control	0.3118	0.0056**	0.0057**	0.0121*
Positive control	0.0133*	0.0027**	0.0063**	0.0955
Antibiotic treatment	0.4226	0.0316*	0.0043**	0.0164*
Herbal extract treatment	0.0153*	0.0389*	0.0088**	0.0205*
Extract treatment with antibiotics	0.0044**	0.0227*	0.0111*	0.0472*

TABLE 5C.

P-value (by number of stars) for the number of macrophages secreted from the wound tissue
on different days (outside the group)

Comparison of groups	1 day	3 day	7 day	14 day	21 day
Negative control \ Positive control	0.0532	0.0027**	0.0051**	0.0123*	0.3333
Positive control \ Antibiotic treatment	0.4226	0.0507	0.0085**	0.0153*	0.0493*
Positive control \ Herbal extract treatment	0.4226	0.0364*	0.0063**	0.0088**	0.4226
Positive control \ Extract treatment with antibiotics	0.4226	0.0129*	0.0056**	0.0344*	0.4226
Antibiotic treatment \ Herbal extract treatment	ns	0.0215*	0.0035**	0.0008***	0.0909
Antibiotic treatment \ Extract treatment with antibiotics	ns	0.0101*	0.0031**	0.0056**	0.0630
herbal extract treatment \ Extract treatment with antibiotics	ns	0.6985	0.0636	0.1271	0.3604

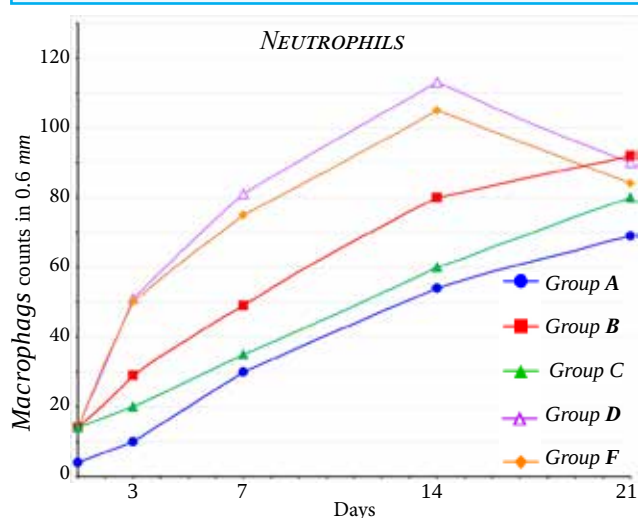


FIGURE 4. Changes in the content of macrophages (in percent) in the studied groups (Group A – Negative control; Group B– Positive control; Group C – Antibiotic treatment; Group D – Herbal extract treatment ; Group F – Extract treatment with antibiotics) on different days.

cerevisiae, and *Saccharomyces carlsbergensis*, and four molds, including *Aspergillus niger*, *Penicillium oxalicum*, *Mucor mucedo*, and *Cladosporium cucumerinum* [Zhu X et al., 2004]. The Minimum inhibitory concentration of the extract was determined by agar and dilution broth methods in the range of 1.25 to 10 mg/mL. The Minimum inhibitory concentration was 2.5 mg/mL against fungi and 2.5 mg/mL against bacteria [Zhu X et al., 2004]. Another study reported that artichoke hydroalcoholic extract inhibited *E. coli* and *S. typhimurium* [Ionescu D. et al., 2013]. In the present study, the minimum lethal and inhibitory concentration was 3.1 mg/mL, which is similar to the presented research. Arbabian et al. studied the antimicrobial effects of aqueous-ethanolic-methanolic and Estonian artichoke extracts on

EXAMINING LYMPHOCYTES SECRETED IN WOUND TISSUE

TABLE 6A.

Mean value and standard deviation for the number of secreted lymphocytes of the wound tissue on different days

Comparison groups	1 day	3 day	7 day	14 day	21 day
Negative control	4.000 ±1.00	6.000 ±1.00	26.00 ±1.500	28.50 ±2.500	26.50±1.500
Positive control	5.000 ±1.00	11.00 ±1.50	25.00 ±2.500	34.00 ±5.000	41.00±4.000
Antibiotic treatment	5.000 ±1.00	5.000 ±0.500	21.00 ±1.000	25.50 ±0.5000	31.00±2.500
Herbal extract treatment	4.000 ±1.00	14.50±0.500	53.50 ±5.500	69.00 ±7.000	65.00±10.50
Extract treatment with antibiotics	4.000 ±1.00	16.00 ±1.00	42.50 ±2.500	63.00 ±6.000	49.00±5.500

TABLE 6B.

P-value (by number of stars) for the number of lymphocytes secreted from the wound tissue on different days (within a group)

Comparison groups	Days within the group			
	1 with 3	3 with 7	7 with 14	14 with 21
Negative control	0.2929	0.0050**	0.2999	0.4453
Positive control	0.0267*	0.0051**	0.0121*	0.0385*
Antibiotic treatment	0.7643	0.0039**	0.0565	0.0389*
Herbal extract treatment	0.0111*	0.0016**	0.0133*	0.0572
Extract treatment with antibiotics	0.0136*	0.0018**	0.0100**	0.0246*

TABLE 6C.

P-value (by number of stars) for the number of lymphocytes secreted from the wound tissue on different days (outside the group)

Comparison of groups	1 day	3 day	7 day	14 day	21 day
Negative control \ Positive control		0.0027**	0.0051**	0.0169*	
Positive control \ Antibiotic treatment	ns	0.0267*	0.0572	0.0169*	0.0194*
Positive control \ Herbal extract treatment	ns	0.0887	0.0028**	0.0016**	0.0017**
Positive control \ Extract treatment with antibiotics	ns	0.0715	0.0008***	0.0059**	0.0299*
Antibiotic treatment \ Herbal extract treatment	ns	0.0028**	0.0031**	0.0007***	0.0009***
Antibiotic treatment \ Extract treatment with antibiotics	ns	0.0082**	0.0027**	0.0030**	0.0061**
Herbal extract treatment \ Extract treatment with antibiotics	ns	0.3118	0.0200*	0.1153	0.0039**

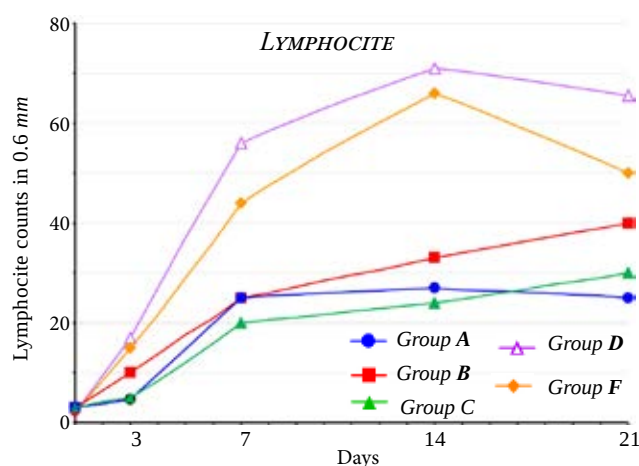


FIGURE 6. Changes in the content of lymphocytes (in percent) in the studied groups (Group A – Negative control; Group B – Positive control; Group C – Antibiotic treatment; Group D – Herbal extract treatment; Group E – Antibiotic treatment with antibiotics; Group F – Extract treatment with antibiotics) on different days.

some bacteria and fungi; the results showed that ethanolic and methanolic extracts of the organs had a growth inhibitory effect on the studied microorganisms. Also, ethanolic extracts prepared from different organs showed a more significant inhibitory effect than methanolic extracts. The inhibitory effect of ethanolic extracts was related to leaves. The highest effect of stem-flower organ extracts and edible part was seen on *S. aureus* and the most negligible effect on *B. cereus*. The highest antifungal effect was related to ethanolic extracts of the studied organs [Ertürk Ö, 2006]. The present study, which used an alcoholic extract presented more effective results, and was similar to the results of another study [Ertürk Ö, 2006].

The present *in vitro* experimental study explored the antimicrobial effectiveness of ethanolic

EXAMINATION OF SECRETED FIBROBLAST IN WOUND TISSUE

TABLE 7A.

Mean value and standard deviation for the number of secreted fibroblasts of wound tissue on different days

Comparison groups	1 dey	3 day	7 day	14 day	21 day
Negative control	5.500 ±0.50	27.50 ±2.50	117.5 ±2.50	97.50 ±2.50	52.50±2.50
Positive control	1.000 ±0.00	6.500 ±1.50	40.50 ±2.50	61.00 ±4.00	65.00±10.00
Antibiotic treatment	1.000 ±0.00	5.000 ±1. 00	36.50 ±1.50	52.50 ±6.50	62.00±5.00
Herbal extract treatment	1.000 ±0.00	27.50 ±2.50	117.5 ±5.50	69.00 ±7.00	15.00±1.00
Extract treatment with antibiotics	1.000 ±0.00	22.50 ±2.50	102.5 ±8.50	46.50 ±2.50	10.00±1.00

TABLE 7B.

P-value (by number of stars) for the number of fibroblasts secreted from the wound tissue on different days (within a group)

Comparison groups	Days within the group			
	1 with 3	3 with 7	7 with 14	14 with 21
Negative control	0.0132*	0.0015**	0.0299*	0.0061**
Positive control	0.0593	0.0022**	0.0030*	0.0572
Antibiotic treatment	0.7643	0.0023**	0.0316*	0.0718
Herbal extract treatment	0.0082**	0.0015**	0.0031**	0.0572***
Extract treatment with antibiotics	0.0121*	0.0019**	0.0027**	0.0028**

TABLE 7C.

P-value (by number of stars) for the number of fibroblasts secreted from the wound tissue on different days (outside the)

Comparison of groups	1 day	3 day	7 day	14 day	21 day
Negative control \ Positive control	0.0082**	0.0187*	0.0011**	0.0054**	0.0377*
Positive control \ Antibiotic treatment	ns	0.4226	0.1271	0.0874	0.0955
Positive control \ Herbal extract treatment	ns	0.0187*	0.0011**	0.0299*	0.0016**
Positive control \ Extract treatment with antibiotics	ns	0.0316*	0.0017**	0.0151*	0.0027**
Antibiotic treatment \ Herbal extract treatment	ns	0.0121*	0.0013**	0.0256*	0.0008***
Antibiotic treatment \ Extract treatment with antibiotics	ns	0.0198*	0.0019**	0.1758	0.0011**
herbal extract treatment \ Extract treatment with antibiotics	ns	0.2929	0.0513	0.0064**	0.1299

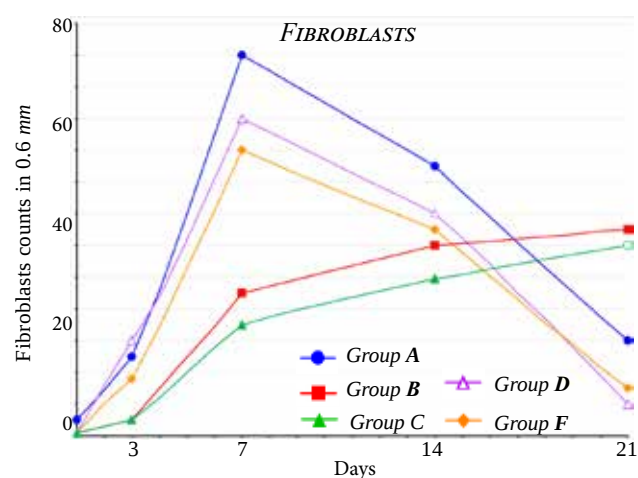


FIGURE 6. Changes in the content of fibroblasts (in percent) in the studied groups (Group A – Negative control; Group B– Positive control; Group C – Antibiotic treatment; Group D – Herbal extract treatment ; Group F – Extract treatment with antibiotics) on different days.

plant extract of *Cynara scolymus* against the target multidrug-resistant *A. Baumannii* infection. In addition, the current study also assessed the synergistic effect of plant extracts in combination with antibiotics against multidrug-resistant *A. Baumannii* infection.

The healing effect of *Cynara scolymus* might be due to several mechanisms such as increasing rate of re-epithelialization and neovascularization, scavenging of destructive free radicals, inflammation reduction and control of infection by the effects of antioxidant, anti-inflammatory and antimicrobial constituents of the plants used in the cream specially polyphenols and tannins as the main components. So, this study confirms the use of *Cynara scolymus* in wound healing in multidrug-resistant *A. Baumannii* infection [Zhu X et al., 2004].

Silver sulfadiazine cream is the most common

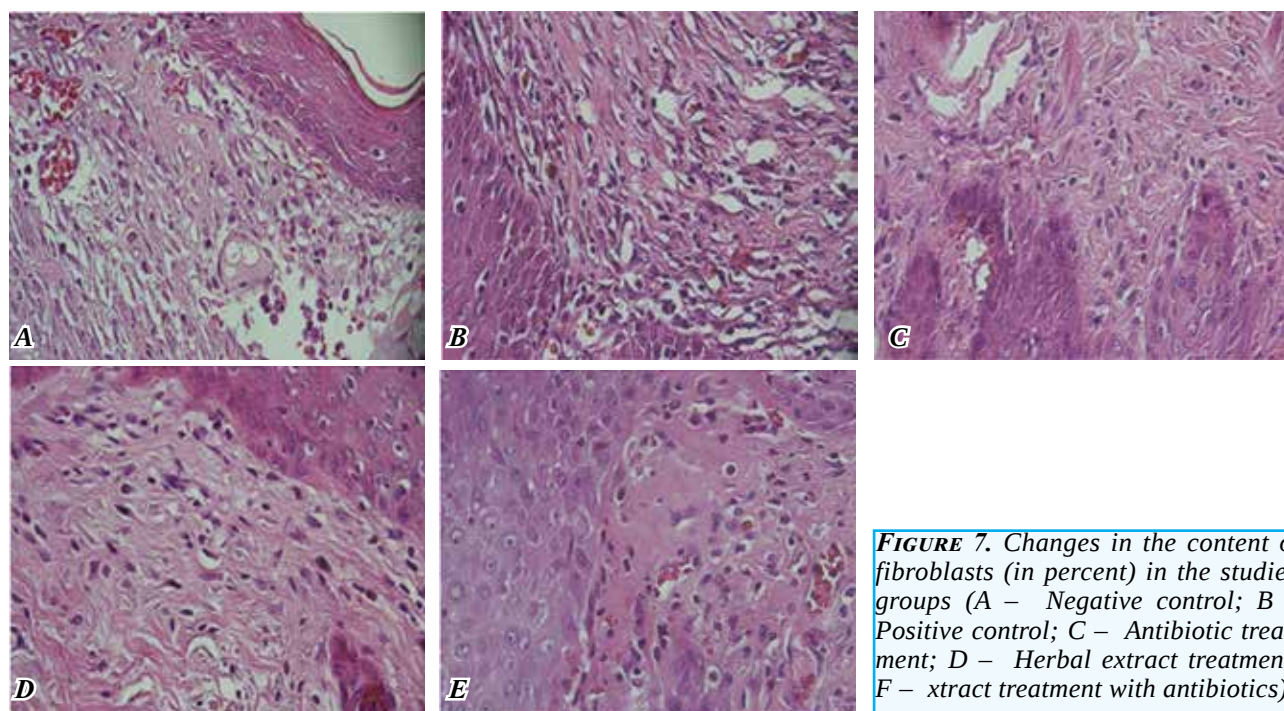


FIGURE 7. Changes in the content of fibroblasts (in percent) in the studied groups (A – Negative control; B – Positive control; C – Antibiotic treatment; D – Herbal extract treatment; E – xtract treatment with antibiotics).

topical product used for treatment of wound injuries. The antimicrobial efficacy of this agent is probably the main reason for its widespread use in wounds. However, delayed wound healing following treatment is the most important clinical adverse effect of silver topical agents which limits their long-term use, especially on broad wounds [Trop M et al., 2006; Thakur R et al., 2011]. According to the current study, in order to achieve the best condition for wound healing in the shortest possible time, the concurrent use of *Cynara scolymus* with SS is suggested during the early stages of wound treatment, while using *Cynara scolymus* alone would be preferable for later stages of treatment period. Due to the angiogenic effect of the cream, diabetic ulcers and bed sore could be good candidates for future studies.

CONCLUSION

Artichoke is a vegetable that is consumed as a food around the world and indicated health-promoting properties in different disease. we have established that not only artichoke contains microbial inhibitors but also that the structures of the antimicrobial compounds isolated from artichoke leaf extract contain microbial inhibitors. The results of the present work indicate that artichoke leaf extracts may be an ideal candidate for further research into their uses for the treatment of Multidrug-Resistant *Acinetobacter Baumannii* infections and merits further studies. as well as pharmaceutical and natural plant-based products.

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